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- (71) Applicant (*for all designated States except US*): ARACHNOVA THERAPEUTICS LTD. [—/—]; 95 Halkett Place, St. Helier, Jersey JE1 1BX (**).
- (72) Inventors; and
- (75) Inventors/Applicants (*for US only*): CAVALLA, David [GB/GB]; Arachnova Ltd., St. John's Innovation Centre, Cambridge CB4 0WS (GB). GRISTWOOD, Robert, William [GB/GB]; Arachnova Ltd., St. John's Innovation Centre, Cambridge CB4 0WS (GB).
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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: NEW THERAPEUTIC USES OF (4-(2-FLUOROPHENYL)-6-METHYL-2-(1-PIPERAZINYL) THIENO[2,3-D]PYRIMIDINE

(57) Abstract: (4-(2-Fluorophenyl)-6-methyl-2-(1-piperaziny)thieno[2,3-D]pyrimidine or a salt thereof has value in the treatment of fibromyalgia, obesity, weight gain and other conditions.

AN2

NEW THERAPEUTIC USES OF 4-(2-FLUOROPHENYL)-6-METHYL-2-
(1-PIPERAZINYL)THIENO[2,3-D]PYRIMIDINE

Field of the Invention

This invention relates to new uses for a known compound.

5 Background of the Invention

A number of non-tricyclic antidepressants have recently been developed that diminish the cardiovascular and anticholinergic liability characteristic of tricyclic antidepressants. These agents include those which inhibit uptake of serotonin and or noradrenaline. A number of uses has been proposed for these agents including the
10 treatment of obesity and weight gain, Parkinson's disease, epilepsy, schizophrenia, obsessive compulsive disorder, substance abuse and drug addiction, pre-menstrual syndrome, eating disorders and migraines and for the encouragement of smoking cessation. Not all non-tricyclic antidepressants work in all disease/conditions and the relative merits of noradrenaline uptake inhibition to serotonin uptake inhibition for each
15 disease/condition is not clear.

(4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine monohydrate hydrochloride is known (see US-A-4695568). It has both serotonin and noradrenergic reuptake blocking properties, but also has important 5HT-3 receptor blocking activity, which would be expected to modify the pharmacological actions of the
20 compound *in vivo* in a non-predictable manner. The utility of this compound in the treatment of pain, of urinary disorders, and of functional bowel disorders has recently been described in WO 02/094249, WO 03/063873 and PCT/GB03/02974, respectively (none published before the first priority date claimed in this case).

Summary of the Invention

25 Surprisingly, it has been found that the known compound identified above (referred to herein as MCI-225) can have valuable activity in the treatment of obesity and weight gain, Parkinson's disease, epilepsy, schizophrenia, obsessive-compulsive disorder, substance abuse, tobacco smoking (encouraging cessation), pre-menstrual syndrome, eating disorders, migraines, recovery from stroke, fibromyalgia, fatigue, nausea, vomiting
30 and emesis including that produced by cancer chemotherapy and radiation therapies. Its combination of serotonin and noradrenergic reuptake blockade and 5HT-3 receptor blockade has not previously been clearly identified as being responsible for these activities.

It will be appreciated that any suitable form of the active principle may be used, e.g. another salt form, or a prodrug or active metabolite.

Description of Preferred Embodiments

By means of this invention, the diseases/conditions outlined above can be treated, e.g. controlled or prevented. A particular embodiment of the invention is in the treatment of fibromyalgia, a chronic condition characterised by fatigue and widespread pain in muscles, ligaments and tendons. This condition was previously known by other names such as fibrositis, chronic muscle pain syndrome, psychogenic rheumatism and tension myalgia.

Another embodiment of the invention lies in a method for treating obesity or weight gain. This means reduction of weight, relief from being overweight, relief from gaining weight, or relief from obesity; all of which are usually due to extensive consumption of food.

Yet another embodiment of the invention lies in a method of treating Parkinson's disease. This means relief from the symptoms of Parkinson's disease which include, but are not limited to, slowly increasing disability in purposeful movement, tremors, bradykinesia, rigidity, and a disturbance of posture in humans.

Yet a further embodiment of the invention lies in a method treating fatigue, including that associated with cancer patients resulting from the disease and/or its treatment, in patients with chronic liver disease including chronic hepatitis C and in patients with chronic fatigue syndrome.

Further embodiments lie in the treatment of obsessive-compulsive disorder, substance abuse, pre-menstrual syndrome, eating disorders and migraine. These terms are used herein in a manner consistent with their accepted meanings in the art. See, e.g. Diagnostic and Statistical Manual of Mental Disorders 4th Ed, American Psychiatric Association (1997).

The terms "method of treating or preventing," "method of treating" and "method of preventing" may be used herein in connection with the disorders to which the invention relates. These terms mean the amelioration, prevention or relief from the symptoms and/or effects associated with these disorders, and are included within the scope of this invention.

For the purposes of this invention, the active compound can be formulated in any suitable manner together with a conventional diluent or carrier. The active compound is

preferably administered by the oral route; other suitable routes of administration include sublingual/buccal, transdermal, intramuscular, intranasal, rectal, parenteral, subcutaneous, pulmonary and topical. An effective dose of the active agent will depend on the nature and degree of the complaint, the age and condition of the patient and other factors known to those skilled in the art. A typical daily dosage may be 0.1 mg to 5 g.

A pharmaceutical composition containing the active ingredient may be in the form of a sublingual tablet or patch. Suitable compositions for oral use include tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups and elixirs. Suitable additives include sweetening agents, flavouring agents, colouring agents and preserving agents. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients, e.g. inert diluents such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated, to form osmotic therapeutic tablets for controlled release. Hard gelatin capsules may include an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin; soft gelatin capsules may include water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

The following Methods are given as examples to illustrate how the beneficial actions of MCI-225 may be demonstrated. Evidence provided in the three recent PCT publications/applications, to which reference is made above, may also be relevant.

Treatment of obesity and weight gain

MCI-225 is evaluated in adult female obese Zucker rats over a period of 32 days. A control group of 6 animals is dosed daily with vehicle alone whilst a second group of 6 weight-matched animals receives MCI-225 at 30mg/kg given orally once daily. Food is available *ad libitum*, except on days 0, 7, 14, 21, 28 and 32 when food was removed from the animals at 7.30 am and animals weighed within 2 hours following removal of food.

Food is supplied after weights of animals are measured. A beneficial effect is demonstrated by the lower body weights of the MCI-225-treated animals.

Treatment of substance abuse/drug addiction

The effects of MCI-225 are determined in alcohol-preferring rats. Because of their
5 pattern of drinking, these animals seem to represent a valid model of the human condition
of alcoholism (McBride *et al*, 1990, Alcohol 7:199-205, Lankford *et al*, 1991, Pharmacol.
Biochem. Behav., 8:293-299). After maximally preferred alcohol concentrations had
stabilised for 4 days, MCI-225 at 30 mg/kg/day orally or vehicle was administered over
4 consecutive days. A beneficial effect of MCI-25 treatment is demonstrated by the
10 reduction in intake of alcohol in terms of absolute g/kg and/or proportion of alcohol to
total fluid intake.

Cessation of smoking

The effects of MCI-225 are investigated in a model of nicotine withdrawal using
the acoustic startle reflex in rats (see e.g. Helton *et al*, 1997, Neuropharmacology 36 (11-
15 12):1511-1516). Nicotine (6 mg/kg/day) is administered for 12 days subcutaneously by
osmotic minipumps. After 12 days, the pumps are removed and the animals allowed to go
through spontaneous withdrawal. Cessation of chronic nicotine exposure leads to
increased startle responses (sensorimotor reactivity) for 4 days following withdrawal. A
beneficial of MCI-225 treatment, for example at 30 mg/kg/day following nicotine
20 withdrawal, is demonstrated by the attenuation of the enhanced auditory startle response
following withdrawal of nicotine.


Treatment of stroke

The effects of MCI-225 are studied in a transient middle cerebral artery occlusion
model in rats (see Chen *et al*, 1999, J. Neurol. Sci. 171(1):24-30). In particular, effects on
25 an array of functional measures are studied, including rotarod, adhesive-backed
somatosensory and neurological scores. A beneficial effect of treatment with MCI-225,
at 30 mg/kg administered for example 2 hours after onset of occlusion, is demonstrated
by improvement in one or more of the functional scores measured following ischaemia
compared with vehicle-treated animals.

30 Treatment of nausea/emesis


The effects of MCI-225 are studied against cisplatin-induced emesis in the ferret
(see Florczyk *et al*, 1982, Cancer Treat. Rep. 66(1):187-189). A beneficial effect of

treatment with MCI-225, at 30 mg/kg orally given 1 hour prior to cisplatin administration, is demonstrated by a reduction in the emetic response compared with control animals. Efficacy against cisplatin predicts efficacy against radiation-induced nausea/vomiting. A wider spectrum of anti-emetic activity of MCI-225 may be demonstrated through the use
5 of other emetogens including apomorphine in the ferret model.



CLAIMS

1. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of fibromyalgia.
2. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or
5 a salt thereof for the manufacture of a medicament for the treatment of obesity and weight gain.
3. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of substance abuse and drug addiction.
- 10 4. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the encouragement of smoking cessation.
5. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of pre-menstrual
15 syndrome.
6. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of eating disorders.
7. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of migraine.
- 20 8. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of Parkinson's disease.
9. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of stroke.
- 25 10. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of nausea and vomiting.
11. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of chemotherapy or
30 radioactivity-induced emesis.
12. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of schizophrenia.

13. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof for the manufacture of a medicament for the treatment of obsessive-compulsive disorder.
 14. Use of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or
5 a salt thereof for the manufacture of a medicament for the treatment of fatigue.
 15. Use according to any of claims 1 to 14, wherein the salt is the hydrochloride monohydrate.
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INTERNATIONAL SEARCH REPORT

 International Application No
 PCT/GB 03/03720

 A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/519 A61P25/06 A61P25/16 A61P25/30 A61P43/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

 Minimum documentation searched (classification system followed by classification symbols)
 IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|---|-----------------------|
| Y | EP 0 150 469 A (MITSUBISHI CHEM IND) 7 August 1985 (1985-08-07) cited in the application table 1-3; page 19 --- | 1-15 |
| Y | EGUCHI JUNICHI ET AL: "Effects of MCI-225 on Memory and glucose utilization in basal forebrain-lesioned rats" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, vol. 51, no. 4, 1995, pages 935-939, XP002257547 ISSN: 0091-3057 page 938-939, paragraph entitled "Discussion" --- -/-- | 1-15 |

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *G* document member of the same patent family

Date of the actual completion of the international search

13 October 2003

Date of mailing of the international search report

10/11/2003

Name and mailing address of the ISA

 European Patent Office, P.O. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax (+31-70) 340-3010

Authorized officer

Borst, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GW 03/03720

| C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT | | |
|--|--|-----------------------|
| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
| Y | EGUCHI J ET AL: "The anxiolytic-like effect of MCI-225, a selective NA reuptake inhibitor with 5-HT3 receptor antagonism" PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR, ELSEVIER, US, vol. 68, no. 4, April 2001 (2001-04), pages 677-683, XP002239887 ISSN: 0091-3057 page 681-682, paragraph entitled "4. Discussion" | 1-15 |
| Y | RAO S G: "THE NEUROPHARMACOLOGY OF CENTRALLY-ACTING ANALGESIC MEDICATIONS IN FIBROMYALGIA" RHEUMATIC DISEASES CLINICS OF NORTH AMERICA, W.B. SAUNDERS, PHILADELPHIA, PA, US, vol. 28, no. 2, 2002, pages 235-259, XP009005801 ISSN: 0889-857X page 246, last full paragraph | 1-15 |
| Y | WO 00 15223 A (IYENGAR SMRITI ;LILLY CO ELI (US); GOLDSTEIN DAVID JOEL (US); SIMM) 23 March 2000 (2000-03-23) page 1, line 17-19; claim 4 | 1-15 |
| Y | WO 02 060427 A (SEPRACOR INC) 8 August 2002 (2002-08-08) page 1, line 7-20; page 7, line 16-26; page 11, line 10-13; page 14, line 11-17 | 1-15 |
| Y | WO 02 064543 A (WYETH) 22 August 2002 (2002-08-22) page 11-17; claim 43, 47 | 1-15 |
| Y | HEAL D J ET AL: "SIBUTRAMINE: A NOVEL ANTI-OBESITY DRUG. A REVIEW OF THE PHARMACOLOGICAL EVIDENCE TO DIFFERENTIATE IT FROM D-AMPHETAMINE AND D-FENFLURAMINE" INTERNATIONAL JOURNAL OF OBESITY, NEWMAN PUBLISHING, LONDON, GB, vol. 22, no. SUPPL 1, August 1998 (1998-08), pages S18-S28, XP008005119 ISSN: 0307-0565 page S26-S27, paragraph entitled "Summary" | 1-15 |
| Y | WO 96 12485 A (LILLY CO ELI) 2 May 1996 (1996-05-02) page 1, line 17-20, claim 1-3 | 1-15 |

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/03720

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☒ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,5,7,14,15(part)

Use of MCI 225 or a salt thereof for the treatment of fibromyalgia, premenstrual syndrome, migraine, fatigue

2. Claims: 2,6,10,11,15(part)

Use of MCI 225 or a salt thereof for the treatment of obesity/weight gain, eating disorders, nausea/vomiting, chemotherapy/radiation induces emesis

3. Claims: 3,4,15(part)

Use of MCI 225 or a salt thereof for the treatment of substance abuse/drug addiction, smoking cessation

4. Claims: 8,9,12,13,15(part)

Use of MCI 225 or a salt thereof for the treatment of Parkinson's disease, stroke, schizophrenia, obsessive compulsive disorders

INTERNATIONAL SEARCH REPORT
on patent family members

International Application No
PCT/JP 03/03720

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|----------------------------|---------------------|
| EP 0150469 | A | 07-08-1985 | JP 1699365 C | 28-09-1992 |
| | | | JP 3067071 B | 21-10-1991 |
| | | | JP 60146891 A | 02-08-1985 |
| | | | AT 35137 T | 15-07-1988 |
| | | | CA 1224782 A1 | 28-07-1987 |
| | | | DE 3472106 D1 | 21-07-1988 |
| | | | DK 617184 A ,B, | 06-07-1985 |
| | | | EP 0150469 A1 | 07-08-1985 |
| | | | HU 37435 A2 | 28-12-1985 |
| | | | US 4695568 A | 22-09-1987 |
| WO 0015223 | A | 23-03-2000 | AU 746887 B2 | 02-05-2002 |
| | | | AU 1197200 A | 03-04-2000 |
| | | | BR 9913671 A | 05-06-2001 |
| | | | CA 2344057 A1 | 23-03-2000 |
| | | | CN 1316904 T | 10-10-2001 |
| | | | EP 1113797 A1 | 11-07-2001 |
| | | | JP 2002524513 T | 06-08-2002 |
| | | | WO 0015223 A1 | 23-03-2000 |
| | | | US 6596756 B1 | 22-07-2003 |
| WO 02060427 | A | 08-08-2002 | US 2002006964 A1 | 17-01-2002 |
| | | | WO 02060427 A2 | 08-08-2002 |
| | | | US 2003078303 A1 | 24-04-2003 |
| WO 02064543 | A | 22-08-2002 | WO 02064543 A2 | 22-08-2002 |
| | | | US 2003045583 A1 | 06-03-2003 |
| WO 9612485 | A | 02-05-1996 | AU 4131296 A | 15-05-1996 |
| | | | WO 9612485 A1 | 02-05-1996 |
| | | | ZA 9508725 A | 16-04-1997 |